REMARKS

Applicants have amended Claims 28, 29 and 37 to track recitations of the claims of an ancestor application, Ser. No. 08/432,483, which is now U.S. Patent 6,410,022. See, in particular, issued Claim 18.* Support for the recitation of "treating or preventing atherosclerosis" is seen at page 24, lines 28-31, of the specification. Support for insertion of the defined term "antigenic" appears at page 10, lines 10-12.

Related Applications and Inventive Feature of the Pending Claims

As noted in Applicants' Preliminary Amendment of August 30, 2001, this application is a division of U.S. application Serial No. 08/945,289, filed October 17, 1997, now allowed and **in issue**, which is a continuation-in-part of and has been terminally disclaimed with respect to U.S. application Serial No. 08/432,483, filed May 1, 1995, now U.S. Patent 6,410,022.

The claims of U.S. Patent 6,410,022 are directed to a particular genus of antigenic vaccine peptides, to the use of such peptides in vaccine compositions, to methods of producing an anti-atherogenic lipoprotein profile, and to methods of treating atherosclerosis in a human or animal using such peptides. The Examiner's attention is directed, in particular, to Claim 18, covering a method of treating atherosclerosis, which is reproduced below in a footnote.

In a manner similar to Claim 18 of U.S. Patent 6,410,022, the amended claims of the instant divisional application cover a method for treating or preventing atherosclerosis in a human or animal comprising administering to the human or other animal an antigenic vaccine peptide comprising:

(1) a helper T cell epitope portion comprising a universal helper T cell epitope, and

(2) a B cell epitope portion comprising a B cell epitope of cholesteryl ester transfer protein (CETP).

The vaccine peptides as recited in the amended claims are "antigenic" as defined on page 10 of the specification, meaning that when administered to a human or animal subject they elicit

* "18. A method of treating atherosclerosis in a human or animal comprising administering to the human or animal an antigenic vaccine hybrid peptide comprising a universal helper T cell epitope portion linked to a B cell epitope portion, wherein said B cell epitope portion comprises six to 26 consecutive amino acids of the carboxyl terminal 26 amino acids of human cholesteryl ester transfer protein."

production of specific antibodies which bind the endogenous CETP of the vaccinated human or animal subject.

The claims as amended thus recite a method of treating atherosclerosis in the exact terms of U.S. Patent 6,410,022, except that the range of CETP B cell epitopes is not confined to the carboxy-terminal 26 amino acids of CETP. The specification of the present application teaches that suitable B cell epitope portions for the vaccine peptides may be selected from other sites on the CETP molecule than the carboxy-terminal portion found to be involved in neutral lipid transfer. For example, use of a B cell epitope corresponding to a triglyceride binding site and/or a cholesteryl ester binding site are expressly taught. See, e.g., page 15, lines 17-25, of the specification. Applicants note that expansion of the scope of the B cell epitope portion to encompass "a B cell epitope portion comprising a B cell epitope of CETP" (i.e., as recited in the present claims as amended) has been determined to be enabled by the present disclosure and to satisfy the written description requirement in the allowed parent case, U.S. application Ser. No. 08/945,289, now in issue.

Therefore, by adopting the terminology of allowed U.S. claims, the present amendments are believed to obviate all of the formal rejections under 35 U.S.C. § 112 that are set forth in the Office Action.

Election of Species

In the Office Action at page 2, the Examiner has made the requirement of election of species final. Applicants acknowledge that the Examiner has reviewed method Claims 28, 29, and 37-39 as they read on the elected species, i.e., on methods for treating atherosclerosis comprising administering a vaccine peptide comprising a helper T cell epitope portion and a B cell epitope portion, wherein the helper T cell epitope portion is derived from tetanus toxoid.

Applicants point out that with respect to embodiments of the elected species wherein the B cell epitope portion is derived from the carboxy-terminal 26 amino acids of human CETP, there is no question of the patentability of the species, because such methods are the subject of a patented claim, namely, Claim 18 of U.S. Patent 6,410,022 (see footnote, *supra*). Thus, the Examiner needs only to consider the patentability of the additional embodiments of the methods encompassed by the elected species.

Updating Status of Related Applications

In the Office Action at page 2, Applicants have been asked to update the present status of the predecessor applications to which the present application claims benefit. Applicants acknowledge the Examiner's instruction to further amend the first paragraph of the application to provide an updated status of the related parent applications U.S. Serial No. 08/432,483, now U.S. Patent No. 6,410,022, and U.S. Serial No. 09/945,289, in issue. Page 1 of the present application has been so amended. The cross-reference will be further updated when the U.S. Patent number for the parent application is known.

Rejections Under 35 U.S.C. § 112, second paragraph

In the Office Action at page 3, Claims 28 and 29 have been rejected under 35 U.S.C. § 112, second paragraph, as having language that is indefinite. In particular, the Examiner states:

> "A). It is improper to recite 'A method for prophylactically treating atherosclerosis in human or other animal in need' in claim 28, line 1. According to Webster's dictionary 'prophylactic' means 'serving against or prevent'. How can one prevent disease in said human or other animal that already has a disease?
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> "B). It is improper to recite 'The method for treating atherosclerosis according to claim 28' in claim 29, line 1. There is insufficient antecedent basis for this limitation in the claim 28. Preamble of Claim 28 recites 'A method for therapeutically or prophylactically treating atherosclerosis.'" (Office Action, paper no. 6, page 3).

Applicants disagree that any person skilled in this art would be prevented from practicing the invention as originally claimed because of the original terminology of the preamble in Claims 28 and 29. However, in any event, this rejection is moot in view of the amendments herein to Claims 28 and 29. The claim language has been amended to track the claim language of U.S. Patent 6,410,022, from which the present application descends.

Accordingly, in view of the amendments to Claims 28 and 29 herein, withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Rejections Under 35 U.S.C. § 112, first paragraph

1. Enablement

In the Office Action at page 4, Claims 28, 29, 37-39 have been rejected under 35 U.S.C. § 112, first paragraph, as lacking an enabling description, requiring undue experimentation, and lacking scope commensurate with the specification, i.e., undue breadth. In view of the amendments to the claims herein, this rejection is believed to be avoided or overcome.

The Examiner's reasons for rejecting Claims 28, 29, and 37-39 under 35 U.S.C. § 112, first paragraph, are provided on pages 3-7 of the Office Action. *Inter alia*, at pages 3-4 of the Office Action, the Examiner states that:

> "Claims 28-29 and 37-39, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method for therapeutically treating atherosclerosis, comprising administrating [sic, all occurrences] a vaccine peptide, consisting of the amino acid sequence of SEQ ID NO:2 or dimer thereof, does not reasonably provide enablement for: (A) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide comprising *any* helper T cell epitope portion and *any* B cell epitope portion of CETP, as recited in claim 28; or (B) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide comprising *any* helper T cell epitope portion derived from an antigenic peptide selected from the group recited in claim 29 and *any* B cell epitope portion of CETP; or (C) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide, comprising *any* helper T cell epitope portion and *any* B cell epitope of CETP, comprising a carboxyl terminal region of human CETP consisting of between 6 and 26 consecutive amino acids of SEQ ID NO:1, as recited in claim 37; or (D) method for therapeutically and prophylactically treating atherosclerosis comprising administrating vaccine peptide comprising amino acid of SEQ ID NO:2, as recited in claim 38, or (E) method for therapeutically and prophylactically treating atherosclerosis comprising administrating vaccine peptide comprising a dimer of the amino acid of SEQ ID NO:2, as recited in claim 39. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims." (italics in original)

Applicants wish to point out that the present claims are not drawn to methods of treating atherosclerosis by administering "*any* vaccine peptide comprising *any* helper T cell epitope portion and *any* B cell epitope portion of CETP." The claims as amended clarify that the present invention is directed to treatment or prevention of atherosclerosis by administration of

> "an antigenic vaccine peptide comprising a universal helper T cell epitope portion linked to a B cell epitope portion, wherein said B cell epitope portion comprises a B cell epitope of CETP." (Claim 28 as amended, emphasis added)

The methods of the present invention employ linked peptides that form a vaccine peptide conjugate having particular properties. Specifically, the vaccine peptides are expressly "antigenic", meaning that when administered in accordance with the claim to a human or animal subject, the peptide elicits an immune response that causes production of native antibodies that recognize the subject's own, endogenous CETP. This is active immunization against a "self" protein (as opposed to a foreign ("non-self") antigen). Applicants, and only Applicants, have demonstrated that such an administration leads to modulation of endogenous CETP activity and in reduction of atherosclerotic lesions in mammalian subjects prone to developing atherosclerosis. (See, Example 10 and Figure 13.)

Thus, the claims require the use of a hybrid peptide in which a universal helper T cell epitope portion and a CETP B cell epitope portion have been judiciously selected and effectively linked, so that they are effective to elicit an antibody response in a vaccinated human or animal subject that leads to modulation of the subject's native (endogenous) CETP activity.

Applicants furthermore invite the Examiner to inspect the claims of U.S. Patent 6,410,022 and U.S. application Ser. No. 08/945,289, both of record, which have been found to be fully enabled by the U.S. Patent Office.

With respect to the standard for an enabling disclosure under 35 U.S.C. § 112, first paragraph, the Examiner's attention is respectfully directed to holdings of the CCPA and its successor court, the CAFC:

> "It has been consistently held that the first paragraph of 35 USC 112 requires nothing more than objective enablement. *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971)."

The law recognizes that an enabling disclosure does not need to describe every possible embodiment covered by the claims:

> "The law does not require the impossible. Hence, it does not require that an applicant describe in his specification every conceivable and possible future embodiment of his invention. The law recognizes that patent specifications are written for those *skilled in the art*, and requires only that the inventor describe the "best mode" known at the time to him of making and using the invention. 35 U.S.C. § 112" *SRI International v. Matsushita Electric Corporation of America*, 775 F.2d 1107, 1121, 227 USPQ 577 (CAFC 1985) (italics and underlining in original).

An objection to the specification as not providing an enabling disclosure cannot be based on broad statements of a conclusion of non-compliance with § 112. On the contrary, to establish a *prima facie* case of non-compliance with 35 U.S.C. § 112, first paragraph, the Examiner must provide **evidence or a reasonable explanation** as to why Applicants' disclosure does not amount to an effective teaching of the invention to a person skilled in the art. As expressed by the Federal Circuit:

> "As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used describing and defining the subject matter sought to be patented **must be taken as in compliance with the enabling requirement** of the first paragraph of § 112 **unless there is reason to doubt the objective truth of the statements contained therein** which must be relied on for enabling support.
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> * * *
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> "In any event, **it is incumbent upon the Patent Office,** whenever a rejection on this basis is made, **to explain** why it doubts the truth or accuracy of any statement in a supporting disclosure and **to back up** assertions of its own **with acceptable evidence or reasoning which is consistent with the contested statement.**" *In re Marzocchi*, 439 F.2d 220, 223-224, 169 USPQ 367, (Fed. Cir. 1971) (emphasis added).

Applicants respectfully submit that the Examiner has not met this standard. The broad conclusory statements of the rejection fail to provide any evidence or reasoning why a person skilled in this art would not accept the entire scope of Applicants' teaching. Accordingly, Applicants assert that a *prima facie* case for lack of an enabling disclosure under 35 U.S.C. §

112, first paragraph, has not been made out; that ample guidance and teaching from the detailed description and working examples has been provided for the skilled artisan to support the entire breadth of the claims; and, finally, that the present claims employ terms and terminology that have already been found, in view of the instant specification, to be fully enabled under U.S. patent law.

For the reasons set forth above, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

2. Written Description

In the Office Action at page 7, Claims 28, 29 and 37-39 have been rejected under 35 U.S.C. § 112, first paragraph, for the reason that the specification is deemed not to reasonably convey to the person skilled in the art that the inventors were in possession of the claimed invention at the time of filing. The Examiner further directs the Applicants to the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description" Requirement, as published in the Federal Register, Vol. 66, No. 4, Jan. 5, 2001, pp. 1099-1111 (hereinafter "Guidelines").

According to those Guidelines, the analysis of possession of the invention is akin to proving complete conception of an invention in an interference:

> "However, it is acknowledged that if evidence typically provided to prove a complete conception is present in the specification as filed, it would be sufficient to show possession. The Federal Circuit has stated '[t]he conception analysis necessarily turns on the inventor's ability to describe his invention with particularity. Until he can do so, he cannot prove possession of the complete mental picture of the invention.' (citation omitted)" (Guidelines at pp. 1101-1102.)

In discussing the General Principles to be applied by Examiners regarding compliance with the written description requirement, the Guidelines state:

> "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as *words*, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including *description of an actual reduction to practice*, or by showing that the invention was 'ready for patenting' such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, *or*

> *by describing distinguishing identifying characteristics* sufficient to show that the applicant was in possession of the claimed invention." (endnotes omitted; italics and underlining added) (Guidelines at p. 1104.)

In the present application, there is an actual reduction to practice of treatment and prevention of atherosclerosis using a vaccine peptide according to the description. The vaccine peptide is identified using a "structural chemical formula", namely, a complete amino acid sequence (SEQ ID NO:2). The use of the vaccine peptide of SEQ ID NO:2 to inhibit formation of atherosclerotic plaque in the aortas of mammalian subjects is described in detail in Examples 6-10 of the specification (pages 32-38). Thus, the specification contains a demonstration of possession of the invention using the primary indicator called for by the Guidelines, namely, "description of an actual reduction to practice."

For any embodiment of the present claims not specifically exemplified in the specification, Applicants have provided a description of "distinguishing identifying characteristics" of the invention, for example, by providing: a complete description of the universal T cell epitope portion of the vaccine peptide; a complete description of the B cell epitope portion of the vaccine polypeptide; a description of methods and materials for linking the two portions; the complete amino acid structures for human and rabbit CETP (SEQ ID NOs:4 and 6); and descriptions of methods for assaying the effectiveness of the vaccine to cause production of endogenous CETP-binding antibodies, to cause increase in HDL-cholesterol levels and/or decrease in free cholesterol or LDL-cholesterol/VLDL-cholesterol levels, and to cause reduction in the formation of atherosclerotic plaque on arterial surfaces. Accordingly, all of the recitations of the claims under examination have been described with such particularity that a person skilled in the art would understand that the inventors were in possession of a full conception of every feature of the invention recited in the claims.

Clearly, the invention as defined in the present claims is supported by sufficient written description in the specification, if the claims are analyzed in accordance with the Guidelines cited by the Examiner.

The Examiner appears to require a written description of the use of every possible embodiment of the vaccine peptide to treat atherosclerosis in order to satisfy the written description requirement under 35 U.S.C. § 112, paragraph 1. A moment's reflection will satisfy

the Director that this is an impossible requirement that is neither required by 35 U.S.C. § 112, first paragraph, nor sought from an analysis of the application conducted under the Guidelines.

Accordingly, for the reasons set forth above, it is respectfully submitted that the present specification provides a written description sufficient to apprise a person skilled in the art that Applicants were in full possession of their invention as of the filing date and that, consequently, the written description requirement of 35 U.S.C. § 112, first paragraph, has been satisfied and the rejection based on that requirement should be reconsidered and withdrawn.

Rejections Under 35 U.S.C. § 103

In the Office Action at page 9, Claims 28, 29, 37 and 38 have been rejected under 35 U.S.C. § 103 as obvious over the combination of:

- Whitlock et al., *J. Clin. Invest.*, 84:129 (1989) ("Whitlock"),

in view of:

- the fact disclosed at page 2, lines 10-12 of Applicants' specification (i.e., the correlation noted in the literature between increased HDL and lowered risk of cardiovascular disease, citing five journal articles),
- Stevens, U.S. Patent 6,143,305 ("Stevens"),
- Swenson et al., *J. Biol. Chem.*, 264:14318 (1989) ("Swenson"), and
- Valmori et al., *J. Immunol.*, 149:717 (1992) ("Valmori").

Applicants traverse this rejection.

Applicants point out, first of all, that the Whitlock, Swenson, and Valmori references were combined and cited against the claims in both U.S. Patent 6,410,022 and the parent case, Ser. No. 08/945,289. The Stevens patent was not cited in the predecessor cases, however the Examiner's attention is drawn to Talwar et al., *Proc. Natl. Acad. Sci. USA*, 91(18):8532 (1994), of record, which was also cited in both earlier cases and which, like Stevens, relates to preparation of a vaccine against human chorionic gonadotropin (hCG) using a compound immunogen composed of a fragment of the endogenous hCG protein and tetanus toxoid. Thus, Talwar et al. may be considered an equivalent reference to the instant Stevens citation. *Cf.*, also, Ladd et al., WO 94/25060 or U.S. Patent 5,843,446, of record, also cited in predecessor cases.

These references, even combined with additional references, have been addressed and overcome by Applicants during prosecution of the predecessor cases.

Whitlock

Whitlock describes a short-term, biochemical study of CETP activity wherein a murine monoclonal antibody reactive with human CETP (i.e., "TP1") is administered to rabbits to study *in vivo* inhibition of CETP activity. Administration of the TP1 antibody, known to inhibit certain CETP functions (see, Hesler et al., *J. Biol. Chem.*, 263:5020 (1988), of record), was shown to inhibit CETP activity in rabbits about 70% immediately after infusion, which inhibition fell to about 44% inhibition after 48 hours (see, e.g., Fig. 2, p. 131 of Whitlock). Applicants specifically note that the Whitlock experiments employ an infusion of pre-made, murine anti-human CETP monoclonal antibody into a rabbit (i.e., passive immunization). There is no teaching or suggestion in Whitlock of actively immunizing an individual against their own CETP.

Stevens

Stevens describes the design and use of a vaccine against establishing pregnancy by attempting to raise antibodies against endogenous chorionic gonadotropin. Example XXXI shows a vaccine construct consisting of a peptide from the β subunit of human chorionic gonadotropin (β-hCG) covalently linked to tetanus toxoid. This human peptide/tetanus toxoid construct was administered to baboons to alter menstrual cycle. Stevens describes various other methods, such as haptenization, of modifying hormones and administering the modified hormones to inhibit hormone activity.

Applicants note that hCG and the other hormones mentioned in Stevens are completely unrelated to CETP, and regulating fertility by immunization is completely different from treating or preventing cardiovascular disease. Stevens does not teach or suggest active immunization against a constitutively produced protein involved in cholesterol metabolism. Stevens does not teach or suggest active immunization against a protein as large as CETP (~70 kD). Stevens does not teach or suggest active immunization against a protein as abundant in circulation as CETP. Stevens does not teach or suggest active immunization to affect circulating cholesterol metabolism or to treat coronary artery disease. And Stevens does not teach or suggest the

concept of actively immunizing an individual against their own CETP or any other protein involved in lipid metabolism.

Swenson

Swenson describes the isolation of a murine monoclonal antibody, designated TP2, that binds to an epitope contained within the carboxy-terminal 26 amino acids of human CETP. Comparative binding assays performed with TP2 indicated that complexing of TP2 with CETP interfered with the neutral lipid binding activity of CETP.

There is no mention in Swenson of the concept of active immunization of an individual to continuously control CETP activity via an endogenous immune response.

Valmori

Valmori describes synthetic multimeric *Plasmodium* antigen constructs which are tested for their ability to raise an antibody response to plasmodium sporozoites and which might therefore be useful as a vaccine protective against malaria. The synthetic constructs of Valmori employ multiple copies of tandem repeat sequences from the circumsporozoite protein from one of two different *Plasmodium* species (i.e., -Asn-Ala-Asn-Pro- or -Asp-Pro-Pro-Pro-Pro-Asn-Pro-Asn), which are made into non-linear tetramers or octamers by attachment to a polylysine core of a multiple antigen peptide (MAP) system (see, e.g., p. 717, right column, and Table II of Valmori).

The experiments reported by Valmori et al. showed that the multimer antigen constructs raised polyclonal antibodies that recognized natural *Plasmodium* circumsporozoite protein; whereas a linear antigen of 40 Asn-Ala-Asn-Pro repeats did not raise an antibody response. See, Table II, p. 718, of Valmori.

Some Valmori constructs also employed one or two tetanus toxoid antigens ("P2" or "P30", Valmori at p. 717, Materials and Methods), and inclusion of either or both of the tetanus antigens increased antibody response.

Valmori is concerned with vaccines against malaria, a disease caused by a parasite. There is no mention in Valmori of the concept of actively immunizing an individual against their own CETP.

The rejection of Claims 28, 29, 37 and 38 for obviousness fails for the following reasons:

1. Any combination of the citations relied on by the Examiner lacks at least one critical factor: There is no indication from any reference that any person skilled in the art has ever conceived of the idea of actively immunizing an individual to modulate the activity of that individual's own CETP *in vivo* with the result of inhibiting arterial plaque formation. That idea came from the inventors only. Thus, there is no substantial evidence of a sufficient motivation or teaching to combine the references relied on by the Examiner to reject Applicants' claims as obvious within the meaning of 35 U.S.C. § 103(a).

2. Even if the references can be considered properly combined, there is more evidence in the prior art of the failure of active immunization to control the activity of an endogenous protein than evidence of success. This being evident from the prior art, and also considering the pronounced differences between CETP and the only self proteins discussed in the citations (i.e., hCG and other hormones), it simply cannot be concluded that a person of ordinary skill in the art prior to Applicants' invention could form a reasonable expectation that atherosclerosis could be successfully treated by active immunization. Thus, the combination of references relied on by the Examiner does not make out a *prima facie* case of obviousness.

3. Even if the references are considered properly combined, and even if a *prima facie* case of obviousness is considered to be made out, the magnitude, duration and effect of the results reported in Applicants' application could not have been expected given the data presented in the prior art, and such unexpected results obtained by Applicants clearly indicate the unobviousness of the presently claimed methods.

The foregoing points are expanded below:

1. Lack of Substantial Evidence of Motivation to Combine the References

Applicants have provided a description of the references combined by the Examiner to reject method Claims 28, 29, 37 and 38 above. None of the references, alone or in combination, provides substantial evidence of a teaching, motivation, or suggestion to be combined to render Claims 28, 29, 37 and 38 *prima facie* obvious under 35 U.S.C. § 103(a).

The legal standard for rejecting claims as obvious over a combination of references was recently reviewed by the Court of Appeals for the Federal Circuit in *In re Kotzab*, 217 F.3d 1365, 55 USPQ2d 1313 (Fed. Cir. 2000). As the court in *Kotzab* noted:

> "A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. See *Dembiczak*, 175 F.3d at 999, 50 USPQ2d at 1617. Close adherence to this methodology is especially important in cases where the very ease with which the invention can be understood may prompt one 'to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher.' *Id.* (quoting *W.L. Gore & Assocs. Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 313 (Fed.Cir.1983)).
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> "Most if not all inventions arise from a combination of old elements. *See In re Rouffett*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457 (Fed.Cir.1998). Thus, every element of a claimed invention may often be found in the prior art. See *Id.* However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. See *Id.* Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant. *See In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed.Cir.1998): *In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed.Cir.1984). . . .
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> "The motivation, suggestion or teaching may come explicitly from statements in the prior art, the knowledge of one of ordinary skill in the art, or, in some cases the nature of the problem to be solved. *See Dembiczak*, 175 F.3d at 999, 50 USPQ2d at 1617. In addition, the teaching, motivation or suggestion may be implicit from the prior art as a whole, rather than expressly stated in the references. *See WMS Gaming, Inc. v. International Game Tech.*, 184 F.3d 1339, 1355, 51 USPQ2d 1385, 1397 (Fed. Cir. 1999). . . . Whether the Board relies on an express or an implicit showing, it must provide particular findings related thereto. *See Dembiczak*, 175 F.3d at 999, 50 USPQ2d at 1617." (*In re Kotzab*, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316-17 (Fed. Cir. 2000) (emphasis added)).

As noted above, the motivation to combine may derive from many sources, however, the range of possible sources that may serve as evidence for a motivation to combine references "does not diminish the requirement for actual evidence. That is, the showing [of a motivation to combine] must be clear and particular." *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617, 1999 WL 246572 (Fed. Cir. 1999) (emphasis added). Furthermore, "[b]road conclusory statements standing alone are not 'evidence.'" *Id.*

Nowhere in the Office Action has the Examiner presented the required evidence of a motivation to combine the cited references to make Applicants' claimed methods *prima facie* obvious. While Swenson may show the use of xenogeneic human CETP or CETP fragments to immunize mice or rabbits and raise murine or rabbit anti-human CETP antibodies for *in vitro* use (e.g., immunoblots, assays, purification protocols), there is no teaching of raising anti-mouse CETP antibodies in mice or anti-rabbit CETP antibodies in the rabbits. In other words, the Examiner's observation of anti-CETP antibodies is not an observation of antibodies raised against endogenous CETP (i.e., as required in the amended claims). Immunization against a foreign CETP has been shown in the references; active immunization against a self CETP has not.

Applicants emphasize that the very idea of devising an immunogen to cause the endogenous CETP of a subject to be recognized by its own antibodies, where it previously was not, is an idea that is utterly absent from the citations of record. Without this spark of motivation, i.e., to consider endogenous CETP as a target for endogenous immune regulation, there is no reason why the hypothetical person of ordinary skill in the art would combine the teachings of the prior art as the Examiner has done.

The Examiner has not shown where the descriptions of these references provide evidence of a motivation or suggestion to be combined with each other to pursue active immunization of an individual to elicit production of autoantibodies that recognize the individual's endogenous CETP and inhibit atherosclerosis.

The references of the Examiner's rejection fall into two categories: CETP references and tetanus toxoid references. The CETP references (Swenson, Whitlock) mention CETP or using human CETP to induce an immune response to human CETP as a foreign antigen in another species (i.e., mice, rabbits). The tetanus toxoid references (Stevens, Valmori) mention the use of

tetanus toxoid to boost immune response against a foreign antigen (*Plasmodium*, Valmori) or against a self antigen (hCG, Stevens).

Although immune response to human CETP as a foreign antigen is described in the CETP references, there is no mention of even the concept of actively immunizing a subject so as to cause its immune system to react against its own CETP. And the tetanus toxoid references do not mention CETP or cardiovascular disease at all. Accordingly, Applicants submit that a bridge between the references does not exist outside Applicants' own specification, and the Examiner cannot point to any evidence in the art prior to Applicants' invention that raises even the concept, let alone the expectation of positive results, that CETP activity within an individual might be modulated by actively causing production *in vivo* of CETP-recognizing endogenous antibodies.

From no combination of these references is the desirability of CETP as an autoimmune target suggested, and even the presence of a reference (Stevens) that involves attempts to raise antigen response to a self antigen does not contain anything to encourage the person of ordinary skill in the art to apply the Stevens disclosure respecting hormones to a completely different class of protein, i.e., a large, constitutively produced, circulating serum protein that plays a role in a complex metabolic cascade, that is, CETP.

The differences between the methods of the invention and the methods of Stevens are too great to admit of any motivation bridging between them. Some differences are summarized below:

		Applicants' Invention	Stevens
1.	area of endeavor	lipoprotein metabolism affecting atherosclerosis	reproductive endocrinology
2.	endogenous antigen target	CETP (476 amino acids in human)	hCG (236 amino acids)
3.	target's expression *in vivo*	constitutive	pulsatile (upregulated only under certain conditions)
4.	concentration of target in plasma	1.87 mg/L - 4.23 mg/L for CETP	< 400 ng/L for hCG
5.	effect of active vaccination	unknown prior to Applicants' work	infertility

In view of the foregoing, Applicants submit that there is no motivation provided by Stevens to the person of ordinary skill in the art to apply its teachings to CETP or to even attempt active vaccination outside the realm of hormone-mediated conditions.

The foregoing provide reasons why the person skilled in the art would NOT be motivated to combine the teachings of Stevens with those of the other citations. In contrast, the Office Action contains no reasons why such a backward motivation would occur.

Applicants respectfully submit that the Examiner has fallen into the trap of hindsight reconstruction by mentally presuming the existence of a motivation or suggestion to combine all references to render Applicants' claimed methods obvious. The Examiner's motivation to combine references is only found in Applicants' own disclosure, which the patent law specifically forbids from being used against Applicants. After reading Applicants' disclosure and working examples, it may seem to the Examiner that others should have earlier conceived of the idea of administering conjugate peptides to produce an anti-atherogenic lipoprotein profile or to inhibit development of atherosclerotic lesions. However, no such teaching or suggestion is found in the citations, alone or in combination, and the Examiner's reasoning rests only on the conclusory statements that motivation exists to tie the references together. Applicants submit

that the Examiner has failed to provide particular evidence for the specific understanding or principles within the knowledge of a person of ordinary skill in the art that would have motivated the person without the benefit of Applicants' disclosure to combine the references cited by the Examiner and to arrive at Applicants' claimed methods. See, *In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000).

Applicants respectfully submit that without identifying with particularity the necessary *evidence* to support a motivation to combine the references as required by law, the combination of the references of record is improper, and the rejection of Claims 28, 29, 37 and 38 should be withdrawn.

2. No Reasonable Expectation of Success is Provided by the References

Even if the references cited by the Examiner are combined, the combination still fails to establish a case of *prima facie* obviousness, because the combination fails to provide a person of ordinary skill in the art with a reasonable likelihood of success for making and carrying out Applicants' claimed invention. This requirement for prior art references used to reject claims as obvious is well established:

> "Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) *whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success*. *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir.1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id.*" *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991) (emphasis added).

The Examiner relies on Stevens for a description of eliciting autoantibodies against endogenous targets. Stevens describes vaccine compositions and methods of use thereof for producing autoantibodies in an individual to inhibit the effect of intermittently produced hormones. No protein mentioned in Stevens has a role in lipoprotein cholesterol metabolism or cardiovascular health. Thus, Applicants submit that a person of ordinary skill in the art would

receive no guidance from Stevens that would be considered relevant or applicable to CETP activity or atherosclerosis.

The Examiner also relies on the study in Whitlock as evidence that a person of ordinary skill in the art would have reasonably expected that Applicants' claimed methods would be effective at altering lipoprotein profiles or decreasing atherosclerotic lesions. Injecting exogenously pre-made antibodies into a subject to obtain a beneficial effect is termed passive immunity, as exemplified by the traditional use of exogenously produced antiserum to snake venom. In contrast, Applicants' claimed methods are methods to produce an active immunity inside an individual, i.e., wherein antigenic vaccine peptides are administered to the individual that are effective at eliciting *endogenous* production of autoantibodies that react with endogenously produced CETP.

The Examiner evidently asserts that combining Whitlock's study using passive immunity with the other references makes Applicants' methods that employ active immunity predictable and, therefore, *prima facie* obvious. However, the fact is that a person of ordinary skill in the art is well aware that passive immunization is NOT a reasonable predictor of active immunization, and *vice versa*.

This lack of predictability between passive immunity and active immunity in an individual is vividly illustrated in Michel et al., *Am. Heart J., 117*: 756-767 (1989), already of record (hereinafter, "Michel"). Michel is a published review of over 30 years of immunologic-based biochemical studies of the renin-angiotensin system (RAS). RAS is a system of at least four distinct proteins (i.e., renin, angiotensinogen, angiotensin-converting enzyme, and angiotensin II) involved in maintaining proper blood pressure. Michel describes how various investigators have attempted over the years to employ antibodies, both exogenously supplied (passive immunity) and endogenously produced (active immunity), as biochemical agents capable of controlling or altering aspects of internal blood pressure regulation. The results obtained in the studies on RAS vary widely and, taken together, illustrate that:

1. the use of passive immunization is not predictive of successful active immunization against a particular protein,

and

2. immunization experiments pertaining to one protein have virtually no value in predicting success of immunization against a different protein.

The examples in Michel demonstrate the above points:

For example, Michel found only one biochemical study on the *in vivo* effects of passive transfer of rabbit antibodies against rat angiotensinogen which suggested angiotensinogen was involved in maintaining blood pressure. However, Michel found no reports of successful active immunization against angiotensinogen using homologous (endogenous) angiotensinogenin in any species in nearly a decade since the study using passive immunity in this well studied field (see, left column, p. 757 of Michel).

In the case of angiotensin-converting enzyme, passive transfer of anti-converting enzyme antibodies could block pressor effect of angiotensins in rats, although immunoallergic responses to the foreign antibodies could quickly lead to death in rabbits. In attempts to actively immunize rats against converting enzyme, only one in 50 animals developed a high specific antibody titer capable of controlling the activity of the endogenous converting enzyme, but that animal died shortly after it was identified (see, right column, p. 757 of Michel).

In the case of angiotensins, some studies using passive transfer of antibodies against angiotensin II showed no effect on blood pressure, while others showed at least a transient result. However, in studies that attempted active immunization against endogenous angiotensin II, only one study in nine showed any effect in controlling blood pressure, even though all reports showed endogenous production of antibodies to angiotensins. Michel opined that such results may indicate that the endogenously produced antibodies lacked sufficient affinity to affect the endogenous angiotensin II (p. 758 of Michel).

In the case of renin, Michel reviewed *in vivo* studies on renin as far back as the 1950's. Studies using passive transfer of anti-renin antibodies yielded variable results depending on the laboratory, suggesting that some exogenously produced anti-renin antibodies were not effective in binding endogenously produced renin. The studies using active immunization against renin were also variable. Michel et al.'s own studies using an animal model indicated that all actively immunized animals developed autoimmune disease (see, p. 763 of Michel).

Applicants respectfully submit that Michel illustrates how variable results have been in attempts to effectively overcome the tolerance of an individual for a particular self protein in order to elicit production of autoantibodies that effectively bind or inhibit the particular endogenously produced protein target. In addition, Michel demonstrates how the results of studies using passive immunity against a protein are not capable of providing the person of ordinary skill in the art with any reasonable basis for predicting the outcome of an attempt to actively immunize an individual against the same protein. Thus, *in the absence of the teachings of Applicants' disclosure*, the Whitlock study using passive immunity would also have been considered by a person of ordinary skill in the art as lacking a reasonable expectation or likelihood of success in the art for methods using active immunization to inhibit CETP and produce a beneficial effect. Accordingly, the passive immunity of the study of the Whitlock reference does not provide a reasonable expectation of success for Applicants' claimed methods that rely on active immunization.

Additionally, the studies reviewed in Michel demonstrate how immunization experiments pertaining to one protein (e.g., angiotensin) cannot be used as a reasonable indication of what to expect regarding immunization for a different protein (e.g., renin). Thus, references such as Stevens that describe results in active immunization of different hormones not only fail as reasonable predictors of success for one another, but also fail to provide any reasonable expectation of success in the making and carrying out of Applicants' claimed methods which involve active immunization against an abundant, constitutively produced, serum protein.

The Examiner is obliged to view the teachings of the prior art in the same way as a person of ordinary skill in the art at the time of Applicants' invention. Whatever else might be determined herein of the level of skill in the art relevant to Applicants' invention, the person of ordinary skill is at least a scientist. Applicants respectfully submit that no scientist could possibly view the results of Stevens and the results reported by Michel (which show immunogenicity differences between protein targets as well as variability between passive vs. active immunization) and then conclude that the prospect of administering a vaccine peptide to an individual to elicit an antibody response capable of modulating the activity of CETP was in any way reasonably to be expected. A scientist would be obliged by the evidence in the art to conclude that no expectation could be formed in advance of the actual experiment to find out if active immunization were possible.

In this case, Applicants were the first to perform that experiment, were the first to demonstrate control of CETP activity by endogenously produced anti-CETP antibodies, and were the first to be able to claim invention of the methods set forth in the pending claims. **There is more evidence from the prior art on this record to conclude that active immunization will fail than there is evidence that it will succeed.** Given the state of the art of immunology, therefore, a person of ordinary skill in the art would never ignore variable data to blindly predict success in an untried field.

Accordingly, Applicants respectfully submit that the Examiner has failed to establish that Applicants' claims are *prima facie* obvious over the combination of references, and the rejection under 35 U.S.C. § 103 should be withdrawn.

3. Applicants' Results Are Unexpected

Even if the references are combined as proposed by the Examiner, the person of ordinary skill in this art could not have expected the results reported by Applicants' claimed methods as demonstrated by the various examples in the specification.

Without the benefit of Applicants' disclosure, it is difficult to believe that a person of ordinary skill in this art would ever expect to design the elected species of conjugate peptide and then successfully carry out the methods of Claims 28, 29, 37 and 38. Following the Examiner's reasoning, the person of ordinary skill in the art would read the cited references and, thereby, be so equipped and enabled, without inventive effort, to design a peptide immunogen including the elected species; to expect such a peptide immunogen would be adequately soluble or dispersible for administration to an individual; to expect that such a peptide immunogen would properly display a helper T cell epitope and a B cell epitope to the immune system in the individual; to expect such a peptide immunogen would be sufficiently stable *in vivo* to elicit an immune response without requiring further modification; to expect that any antibody produced in such an immune response would not only recognize the peptide immunogen but would also bind the native, endogenously produced, circulating CETP; to expect that such a sustained immune response would only affect CETP activity without destruction of tissues and organs; to expect that such an immune response would produce sufficient levels of antibody that would effectively modulate the activity of the relatively high, constitutive, circulating levels of endogenous CETP as opposed to the transient, low levels of hormone peptides described in Stevens; to expect that

such an immune response would continue to modulate endogenous CETP without diminishing in 48 hours as in Whitlock; and to expect that such an immune response to endogenous CETP would alter lipoprotein levels and inhibit development of atherosclerotic lesions to provide actual tissue benefit and not tissue destruction.

Applicants submit that this string of expectations which the Examiner ascribes to a person of ordinary skill in the art not only outstrips the expectations of the Applicants themselves prior to their inventive work but makes the person of ordinary skill in the art, in this case, the most prescient scientist of all time. But even presuming this level of expectation, i.e., that the best results of all the references would be realized in the field of Applicants' invention, the results predicted by the combined citations would only lead to the expectation of a transient reduction of CETP activity, e.g., reduction of a matter of hours as in Whitlock, which would be overcome by clearance of the antibodies or possibly neutralized by upregulation of CETP production *in vivo*. Applicants' results show that the actual performance of this work produced an antibody response that was specific (Example 6) and which produced lasting effects on cholesterol and HDL levels in vaccinated individuals (Figs. 11 and 12).

Moreover, there is no way for a person of ordinary skill in the art to form an expectation as to the results of vaccination on the extent of development of atherosclerotic lesions, because none of the references includes any teachings that link plasma effects with physiological effects. Thus, Applicants' Example 10 and Fig. 13, which show the effect of their observed degree of modulation of endogenous CETP activity on the reduction of atherosclerotic lesions, present results that are clearly unexpected and unpredictable on the basis of the prior art.

For the foregoing reasons, Applicants' invention as recited in the claims is unobvious in view of the citations of record, and the rejection of those claims must be withdrawn.

In the Office Action at page 11, Claim 39 has been rejected as obvious over the combination of Whitlock in view of the fact disclosed at page 2, lines 10-12 of Applicants' specification, Stevens, Swenson and Valmori as applied to Claims 28, 29, 37 and 38, further in view of either Talwar et al., *Proc. Natl. Acad. Sci. USA,* 91:8532-36 (1994) or Stanton et al., U.S. Patent 5,807,552. The Examiner asserts that from either Talwar et al. or Stanton et al., it would have been obvious for a person of ordinary skill in the art to dimerize a peptide immunogen.

This rejection is traversed.

Since the Talwar et al. and Stanton et al. references are only relied on to show that dimerization of a peptide immunogen is not novel, Applicants will not review the teachings of the references or their non-applicability to the present invention. The rejection of Claim 39 fails because the combination of primary and secondary references (i.e., Whitlock in view of the fact disclosed at page 2, lines 10-12 of Applicants' specification, Stevens, Swenson and Valmori) fails to render the method of treatment invention obvious, for the reasons set forth in detail above. The disclosures of Talwar et al. and Stanton et al. with respect to dimerization do nothing to overcome the insufficiency of the primary and secondary references to motivate the performance of a method according to the invention, to reasonably expect successful treatment of atherosclerosis by that method, or to predict the unexpected results obtained by Applicants in inhibiting formation of atherosclerotic lesions. There is furthermore no teaching in Talwar et al. or Stanton et al. that links dimerization to successful treatment of atherosclerosis. Thus, the additional citation of the tertiary references does not render the *method* of any of the claims obvious.

For the foregoing reasons, the rejection of Claim 39 under 35 U.S.C. § 103 should be withdrawn.

Obviousness Type Double Patenting

In the Office Action at page 12, the claims have been rejected under the judicially created doctrine of obviousness-type double patenting in view of the commonly assigned predecessor patent, U.S. Patent 6,410,022.

The Examiner notes that this rejection may be overcome by submission of a terminal disclaimer. A terminal disclaimer is submitted herewith. Entry of the terminal disclaimer and removal of the rejection are therefore respectfully requested.

For the foregoing reasons, and in view of the claim amendments above, Applicants believe that all rejections set forth in paper no. 6 have been obviated or overcome, and therefore entry of the amendments and allowance of all claims are respectfully requested.

Applicants have filed an Information Disclosure Statement and a PTO Form 1449 with the original application papers. Acknowledgement of the citations and that the publications thus cited are of record herein is requested.

Respectfully submitted,

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CERTIFICATE OF MAILING

The undersigned hereby certifies that this correspondence is being deposited with the U.S. Postal Service as First Class mail under 37 C.F.R. §1.8, postage prepaid, in an envelope addressed to the Commissioner for Patents, Washington, D.C. 20231 on the date indicated below:

January 30, 2003
date of mailing and signature

Leon R. Yankwich

Marked Up Version of Replacement Paragraph on Page 1 Pursuant to 37 C.F.R. § 1.121(b)

--This application is a divisional ~~application~~ of U.S. application Serial No. 08/945,289, filed October 17, 1997, in issue, which is ~~the United States national stage under 35 U.S.C. § 371 of international application No. PCT/US96/06147, filed May 1, 1996, which is~~ a continuation-in-part ~~application~~ of U.S. application Serial No. 08/432,483, filed May 1, 1995, now U.S. Patent 6,410,022.--

Marked Up Version of Amended Claims Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

28. (amended) A method for ~~therapeutically or prophylactically~~ treating or preventing atherosclerosis in a human or ~~other~~ animal ~~in need of treatment thereof~~ comprising administering to said human or ~~other~~ animal ~~a~~ an antigenic vaccine peptide ~~in a pharmaceutically acceptable buffer, said vaccine peptide~~ comprising a universal helper T cell epitope portion ~~comprising a helper T cell epitope and~~ linked to a B cell epitope portion, wherein said B cell epitope portion comprises ~~comprising~~ a B cell epitope of CETP.

29. (amended) The method ~~for treating atherosclerosis~~ according to claim 28, wherein said helper T cell epitope portion comprises a helper T cell epitope derived from an antigenic peptide selected from the group consisting of tetanus toxoid, diphtheria toxoid, pertussis vaccine, Bacile Calmette-Guerin (BCG), polio vaccine, measles vaccine, mumps vaccine, rubella vaccine, purified protein derivative of tuberculin, keyhole limpet hemocyanin, hsp70, and combinations thereof.

37. (amended) The method according to claim 28, wherein ~~the~~ said B cell epitope portion of the antigenic vaccine peptide comprises ~~a carboxyl terminal region of human CETP consisting of between~~ 6 ~~and~~ to 26 consecutive amino acids of the carboxyl terminal 26 amino acids of human cholesteryl ester transfer protein (SEQ ID NO:1).